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Does setting the breathing machine (ventilator) to deliver breaths using a method called airway pressure release ventilation help patients with diseased lungs to heal faster and spend less time on a ventilator?

Submission date
12/06/2024

Registration date
21/06/2024

Last Edited
25/06/2025

Recruitment status
Recruiting

Overall study status
Ongoing

Condition category
Respiratory

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims

Around half of all patients in critical care need help from a breathing machine (ventilator) to maintain oxygen levels. Although they may be life-saving, breathing machines can cause damage to diseased lungs and make chest infections more likely.

The usual way a breathing machine is used aims to protect the lungs from damage until they are healed. However, damage can still occur, and the lungs take time to recover. Airway pressure release ventilation (APRV) is a way of using the breathing machine that we think causes less damage. It moves gas into the lungs gently over a longer time. This helps to reduce lung damage, helping faster healing. APRV may reduce time on the breathing machine and in the hospital which may save costs. APRV may also reduce the risk of death.

The aim of this study is to find out if setting the breathing machine to deliver breaths using APRV helps patients with diseased lungs to heal faster and spend less time on a ventilator compared to the usual way breathing support is given in critical care. The researchers also want to know if APRV saves more lives, improves quality of life, and saves the NHS money by helping people leave CCU sooner.

Who can participate?

Patients admitted to a CCU in the UK who are:

1. Aged 18 years or more
2. Receiving support from a breathing machine
3. Have moderate to severely low oxygen levels
4. Are expected by the critical care team to stay on a breathing machine for more than 2 days

What does the study involve?

Participants will be assigned by chance (randomised) to one of two groups.

1. APRV: The breathing machine will be set to the APRV mode. APRV moves gas into the lungs

gently over a longer time. APRV is available on all ventilators that are used within the NHS.
2. Usual care: The breathing machine will be set as usual by the critical care team.
There will be no other changes to care delivered by the critical care team for patients in both the APRV and usual care group.
Participants, the research team, or the critical care team will not be able to choose which group your relative/friend is in. This is decided by a computer at random, just like tossing a coin or drawing lots.
The research team will collect information about the care the participants receive while in critical care including how the breathing machine is used, how long they need the machine, and how long they stay in critical care. The research team will collect the participants' personal information such as age, ethnicity, sex and past medical conditions before coming to critical care as this helps them to understand the effect of APRV on different groups of people.
After leaving the hospital, participants will be sent a questionnaire 2 and 6 months after hospital discharge asking about their overall wellbeing and quality of life. Each questionnaire will take about 5 to 10 minutes to complete. If needed, someone can complete them on the participant's behalf. The researchers will share the participant's name, email address, and phone number with a third-party company in order to send them the questionnaires by text message or email. They may also get in touch with participants by text message or email if we have any queries about their questionnaire or if we have any updates related to the study.

What are the possible benefits and risks of participating?
As this is a study, participants may or may not benefit from taking part. However, the findings of the research will help to improve the treatments and care provided to patients with a similar condition now and in the future.
There is no payment for taking part in this study. However, to thank participants for their time in completing the follow-up questionnaires at 2 and 6 months, they will be given a small monetary gift voucher alongside each questionnaire.
The University of Warwick is currently leading several studies looking at how we treat patients with respiratory failure. This group of studies is called the 'Confederation of Respiratory Critical Care Trials' or 'CoReCCT'. If participants are taking part in other studies within CoReCCT, they will not need to complete questionnaires for each study. Participants will only be asked to complete the questionnaires once and will receive one voucher with each questionnaire.
At this time, there are no important disadvantages or risks to taking part.

Where is the study run from?
Warwick University in partnership with NHS hospitals across the UK

When is the study starting and how long is it expected to run for?
January 2024 to August 2027

Who is funding the study?
National Institute for Health Research, Health Technology Assessment (NIHR154501) (UK)

Who is the main contact?
RELEASE trial manager, RELEASE@warwick.ac.uk

Study website
https://warwick.ac.uk/fac/sci/med/research/ctu/trials/release/

Contact information

Type(s)
Scientific, Principal Investigator

Contact name
Prof Luigi Camporota

ORCID ID
https://orcid.org/0000-0001-5600-1676

Contact details
Department of Critical Care
Guy’s & St Thomas’ NHS Foundation Trust
Westminster Bridge
London
United Kingdom
SE1 7EH
-
release@warwick.ac.uk

Type(s)
Scientific, Principal Investigator

Contact name
Prof Danny McAuley

ORCID ID
https://orcid.org/0000-0002-3283-1947

Contact details
Wellcome-Wolfson Institute for Experimental Medicine
The Queen's University of Belfast
Belfast
United Kingdom
BT9 7BL
-
release@warwick.ac.uk

Type(s)
Public, Scientific

Contact name
Mr Jonathan Guck

Contact details
Warwick Clinical Trials Unit
Warwick Medical School
University of Warwick
Gibbet Hill Road
Coventry
United Kingdom
CV4 7AL

+44 (0)2476 575 194
release@warwick.ac.uk

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
335630

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
IRAS 335630, NIHR154501, CPMS 62929

Study information

Scientific Title
Airway Pressure Release Ventilation (APRV) vs conventional ventilation for patients with moderate to severe acute hypoxemic respiratory failure: the RELEASE trial

Acronym
RELEASE

Study objectives
What is the clinical and cost-effectiveness of airway pressure release ventilation (APRV) for adults requiring invasive mechanical ventilation (IMV) for moderate-severe acute hypoxaemic respiratory failure (AHRF)?

Ethics approval required
Ethics approval required

Ethics approval(s)
1. Approved 08/07/2024, Wales REC 2 (The Cardiff North Inn by Accor, Circle Way East, Llanaderyn, Cardiff, CF23 9XF, United Kingdom; +44 (0)2922941119; Wales.REC2@wales.nhs.uk), ref: 24/WA/0128

2. Submitted 18/06/2025, Scotland A REC (NHS Lothian , Edinburgh, EH1 3EG, United Kingdom; +44 131 465 5680; Manx.Neill@nhslothian.scot.nhs.uk), ref: 25-SS-0056-IRAS-351070

Study design
Multi-centre randomized allocation-concealed controlled open-label pragmatic parallel-group clinical and cost-effectiveness trial with an internal pilot

Primary study design
Interventional

Secondary study design

Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
See study outputs table

Health condition(s) or problem(s) studied
Moderate to severe acute hypoxaemic respiratory failure (AHRF)

Interventions
Participants are randomised to either:
1. Early airway pressure release ventilation (APRV)
2. Standard conventional lung protective invasive mechanical ventilation (no APRV)

Participants will be randomised via randomly permuted blocks using an automated web-based system on a one-to-one basis, stratified by site and prior enrolment into the Awake Prone Positioning and Protect Airways trials, using a computer-generated randomisation schedule managed by the Warwick CTU. The researchers have selected a parallel group RCT design to minimise selection bias and ensure against accidental bias.

The intervention (APRV or control) will continue until one of the following criteria is met:
1. 60 days after randomisation
2. Successful unassisted breathing (at 48 hours with no further requirement for inspiratory support or extracorporeal lung support. See section 2.4.3 for the full definition)
3. Trial intervention-related serious adverse event
4. Death or discontinuation of active treatment
5. Withdrawal of consent

Intervention Type
Other

Primary outcome measure
Current primary outcome measure as of 25/06/2025:

Duration of mechanical ventilation (defined as the time from randomisation to first successful unassisted breathing or death) measured using data collected from site staff at the time of first successful unassisted breathing or death

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Previous primary outcome measure:

Duration of invasive mechanical ventilation (defined as the time from randomisation to first successful unassisted breathing or death) measured using data collected from site staff at the time of first successful unassisted breathing or death

Secondary outcome measures
Current secondary outcome measures as of 25/06/2025:

1. All-cause mortality measured using data collected from site staff at 2 and 6 months
2. Time to first successful extubation
3. Need for reintubation prior to achieving first successful unassisted breathing
4. Use of non-invasive ventilation following extubation but prior to achieving first successful unassisted breathing
5. CCU and hospital length of stay measured using data collected from site staff at time of CCU and hospital discharge
6. Serious adverse events measured using data collected from site staff up to time of hospital discharge
7. Health-related quality of life measured using the 5-level EQ-5D version (EQ-5D-5L) at 2 and 6 months
8. Acute health care use measured using participant-completed resource use questionnaires and, if available, enriched using data obtained from site staff or linkage at 2 and 6 months
9. Within-trial cost-utility analysis from an NHS hospital care perspective using data collected from site staff and data obtained through linkage to routine datasets at 2 and 6 months

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Previous secondary outcome measures:

1. All-cause mortality measured using data collected from site staff at 2 and 6 months
2. Time to first extubation measured using data collected from site staff at time of extubation
3. Reintubation measured using data collected from site staff at time of reintubation
4. Use of non-invasive ventilation following extubation measured using data collected from site staff at time of extubation
5. CCU and hospital length of stay measured using data collected from site staff at time of CCU and hospital discharge
6. Serious adverse events measured using data collected from site staff up to time of hospital discharge
7. Health-related quality of life measured using the 5-level EQ-5D version (EQ-5D-5L) at 2 and 6 months
8. Acute health care use measured using participant-completed resource use questionnaires and, if available, enriched using data obtained from site staff or linkage at 2 and 6 months
9. Within-trial cost-utility analysis from an NHS hospital care perspective using data collected from site staff and data obtained through linkage to routine datasets at 2 and 6 months

Overall study start date
01/01/2024

Completion date
31/08/2027

Eligibility

Key inclusion criteria
Current inclusion criteria as of 25/06/2025:

1. Age ≥18 years
2. Receiving invasive mechanical ventilation
3. Moderate to severe acute hypoxaemic respiratory failure, defined as a single measurement showing a PaO_2/FiO_2 ratio <20 kPa while receiving a Positive End-Expiratory Pressure (PEEP) of ≥5 cmH_2O, assessed at any point within the first 60 hours after the initiation of invasive mechanical ventilation
4. Expected to stay on invasive mechanical ventilation for >48 hours

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Previous inclusion criteria:

1. Age ≥18 years
2. Receiving invasive mechanical ventilation
3. Moderate to severe AHRF (PaO2/FiO2 <20 kPa with Positive End Expiratory Pressure (PEEP) ≥5 cmH2O) assessed at the time of screening (or as documented in the medical record in the preceding 2 hours)
4. Expected to stay on invasive mechanical ventilation for >48 hours

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
710

Key exclusion criteria
Current exclusion criteria as of 25/06/2025:

1. Receiving IMV ≥60 hours at the time of screening as will be unable to deliver early APRV
2. Primary reason for invasive mechanical ventilation is one of the following:
2.1. Asthma
2.2. Severe COPD
2.3. Pulmonary embolism (massive or sub-massive) (as cause of hypoxaemia is not primarily due to collapse of lung tissue)
2.4. Existing neuromuscular disease such as motor neurone disease, Guillain Barre or myasthenia gravis (as the cause of respiratory failure is not primarily lung-related)
3. Refractory shock (systolic blood pressure < 90 mmHg, despite fluid administration and vasoactive drugs)*
4. Severe hypercapnic respiratory acidosis (pH <7.20 on the arterial blood gas assessed for trial inclusion)*
5. Ongoing air leak (e.g. unresolved pneumothorax at time of screening)*
6. Traumatic brain injury with uncontrolled intracranial hypertension*

7. Likely death or treatment withdrawal in the next 24 hours
8. Home ventilation or home oxygen therapy prior to admission
9. Receiving, or decision to commence, ECMO in the next 24 hours
*(patients can be recruited if this resolves and remain eligible)

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Previous exclusion criteria:

1. Receiving IMV ≥60 hours at the time of screening as will be unable to deliver early APRV
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2.1. Asthma
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2.3. Pulmonary embolism (massive or sub-massive) (as cause of hypoxaemia is not primarily due to collapse of lung tissue)
2.4. Existing neuromuscular disease such as motor neurone disease, Guillain Barre or myasthenia gravis (as the cause of respiratory failure is not primarily lung-related)
3. Refractory shock (systolic blood pressure < 90 mmHg, despite fluid administration and vasoactive drugs)*
4. Severe hypercapnic respiratory acidosis (pH <7.20 on the arterial blood gas assessed for trial inclusion)*
5. Ongoing air leak (e.g. unresolved pneumothorax at time of screening)*
6. Traumatic brain injury with uncontrolled intracranial hypertension*
7. Likely death or treatment withdrawal in the next 24 hours
8. Home ventilation or home oxygen therapy prior to admission
*(patients can be recruited if this resolves and remain eligible)

Date of first enrolment
14/02/2025

Date of final enrolment
31/05/2027

Locations

Countries of recruitment
England

Northern Ireland

Scotland

United Kingdom

Wales

Study participating centre
Guy's and St Thomas' NHS Foundation Trust
St Thomas' Hospital

Westminster Bridge Road
London
United Kingdom
SE1 7EH

Study participating centre
Arrow Park Hospital
Arrowe Park Hospital
Arrowe Park Road
Wirral
United Kingdom
CH49 5PE

Study participating centre
Bedford Hospital
Icash Bedford Hospital
Kempston Road
Bedford
United Kingdom
MK42 9DJ

Study participating centre
University Hospital Bristol
Bristol Royal Infirmary
Marlborough Street
Bristol
United Kingdom
BS2 8HW

Study participating centre
Conquest Hospital
The Ridge
St. Leonards-on-sea
United Kingdom
TN37 7RD

Study participating centre
Queen Alexandras Hospital
Southwick Hill Road
Cosham
Portsmouth

United Kingdom
PO6 3LY

Study participating centre
Tameside General Hospital
Fountain Street
Ashton-under-lyne
United Kingdom
OL6 9RW

Study participating centre
Blackpool Teaching Hospitals NHS Foundation Trust
Victoria Hospital
Whinney Heys Road
Blackpool
United Kingdom
FY3 8NR

Study participating centre
Ipswich Hospital Utc
Ipswich Hospital
Heath Road
Ipswich
United Kingdom
IP4 5PD

Study participating centre
James Cook University Hospital
Marton Road
Middlesbrough
United Kingdom
TS4 3BW

Study participating centre
Kingston Hospital
Galsworthy Road
Kingston upon Thames
United Kingdom
KT2 7QB

Study participating centre
Medway NHS Foundation Trust
Medway Maritime Hospital
Windmill Road
Gillingham
United Kingdom
ME7 5NY

Study participating centre
Russells Hall Hospital
Pensnett Road
Dudley
United Kingdom
DY1 2HQ

Study participating centre
Queen Elizabeth Hospital Lewisham
Stadium Road
London
United Kingdom
SE18 4QH

Study participating centre
St Georges Hospital
Blackshaw Road
Tooting
London
United Kingdom
SW17 0QT

Study participating centre
Aintree University Hospital
Lower Lane
Liverpool
United Kingdom
L9 7AL

Study participating centre
University Hospital Lewisham
Lewisham High Street

London
United Kingdom
SE13 6LH

Study participating centre
University Hospital of North Tees
Hardwick Road
Hardwick
Stockton-on Tees
United Kingdom
TS19 8PE

Study participating centre
William Harvey Hospital
Kennington Road
Willesborough
Ashford
United Kingdom
TN24 0LZ

Study participating centre
Milton Keynes University Hospital
Standing Way
Eaglestone
Milton Keynes
United Kingdom
MK6 5LD

Study participating centre
University Hospitals Plymouth NHS Trust
Derriford Hospital
Derriford Road
Derriford
Plymouth
United Kingdom
PL6 8DH

Sponsor information

Organisation

University of Warwick

Sponsor details
Research and Impact Services
University House
Gibbet Hill Road
Coventry
England
United Kingdom
CV4 8UW
+44 (0)2476 575 733
sponsorship@warwick.ac.uk

Sponsor type
University/education

Website
https://warwick.ac.uk/fac/sci/med/research/ctu/

ROR
https://ror.org/01a77tt86

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme

Alternative Name(s)
NIHR Health Technology Assessment Programme, HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan

Planned publication in a peer-reviewed journal. The researchers will use a multi-modal dissemination strategy: open access publication in high-impact factor journals; presentation at relevant national/international scientific conferences; and communication with participant and family networks including social media and lay press with a lay results summary to participants.

Intention to publish date
31/08/2028

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 2.0	13/06/2024	16/07/2024	No	No
Participant information sheet			25/06/2025	No	Yes
Protocol file	version 3.0	26/03/2025	25/06/2025	No	No